## REMARKS

### I. Petition for Extension of Time

Applicants herewith petition the Commissioner for Patents to extend the time for response to the Office Action mailed March 2, 2004 for two months from June 2, 2004 to August 2, 2004. Authorization is given to charge the extension of time fee of $420.00 (37 C.F.R. §§1.136 and 1.17) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

### II. Rejection under 35 U.S.C. § 103(a)

Claims 1-10 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over US 3,442,686 to Jones ("Jones") in view of the combination of US 3,967,728 to Gordon et al. ("Gordon") and US 4,585,666 to Lambert ("Lambert").

The obviousness rejection is based on the allegation that it would have been obvious to use the packaging film disclosed by the primary reference to Jones as a barrier material in ethylene oxide ("EO") sterilization of medical devices. Specifically, Jones discloses a film comprising an inorganic glassy barrier composition, e.g., silicon dioxide ($SiO_2$), sandwiched between an organic base film and a sealable topcoat.

The secondary reference to Gordon discloses a catheter package comprising a pouch **17** containing a sterile lubricant. Gordon expressly states that "the outer covering of the pouch **17** is preferably a gas impermeable material since sterilizing gases such as ethylene oxide may have a deleterious effect upon the lubricant". (col. 3, lines 45-48). The only gas impermeable material (**36, 38**) disclosed by Gordon is a metal or aluminum foil. (col. 2, lines 49-50).



PAGE 2/8 * RCVD AT 7/27/2004 10:13:37 AM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:2123548131 * DURATION (mm-ss):02-40

It is well-known that EO is very reactive because its highly strained ring can be easily opened. Moreover, it is well-known and well-documented that EO sterilization affects the characteristics and properties of plastics and elastomers, and can cause deterioration of the polymer. The secondary reference to Gordon has no reason to be concerned with such EO reactivity since the interior thermoplastic sheets (**35, 37**) of the pouch **17** are protected from contact with EO by the gas impermeable metal or aluminum foil (**36, 38**) overlaying the interior thermoplastic sheets.

In contrast to Gordon, there is no protective metallic or aluminum foil overlaying and protecting the organic polymer layers of the packaging film of Jones. As such, the gas impermeable metallic/aluminum foil (**36, 38**) disclosed by Gordon is structurally and fundamentally different from the packaging film disclosed by Jones. Therefore, if the packaging film disclosed by Jones were to be used as a barrier material in EO sterilization, the EO gas and residual EO could have a deleterious effect during sterilization and storage on the characteristics and properties of the organic polymer layers of the packaging film.

Proper and safe EO sterilization of medical devices require careful monitoring and selection of packaging materials and sterilization parameters (See Medical Plastics: Data Services, http://www.medicalplasticsindia.com/mpds/2002/may/packaging.htm ["Medical Plastics"], copy attached). The Examiner acknowledged in the Office Action (Paper No. 16), mailed November 4, 2002, that "Jones fails to explicitly teach the specific type of gas such as ethylene oxide". As such, there is no appreciation by Jones of the potentially deleterious effect of EO and EO residuals on the properties, characteristics and physical integrity of the non-metallic, aluminum-free packaging film which he discloses.

Without further disclosure, one of ordinary skill could not know whether the laminate of Jones is stable in the presence of strongly aggressive sterilizing gases such as EO. Rather, based on the known reactivity of EO, one could reasonably expect that exposure to EO would weaken the laminate and significantly affect its barrier properties, for example, by becoming cracked, hazed, or crazed. Furthermore, one could reasonably expect that the lifespan of the laminate would be drastically reduced after exposure to EO, for example, from years under "normal conditions" to just a few months.

The apparent lack of knowledge and awareness demonstrated by Jones with specific regard to EO sterilization is in stark contrast to the high standards required by the medical and health-care industry. There is no suggestion that the barrier material of Jones could be successfully used in medical applications. It is well known that materials for medical applications must have a higher threshold of safety and stability than materials which may not be specifically designed for medical use. As stated by Medical Plastics, "[f]or proper and safe ETO [ethylene oxide] sterilization of medical devices, packaging materials and sterilization parameters go together. They need careful monitoring and selection."

For all of the foregoing reasons, Applicants submit that there is no motivation or suggestion to replace the gas impermeable metallic/aluminum foil (**36, 38**) disclosed by Gordon with the packaging film of Jones as a barrier material in any method involving EO sterilization of medical devices. In view of the well-known and documented effects of EO sterilization on the characteristics and properties of plastics and elastomers, it was indeed unexpected that the laminate recited in claim 1 was relatively unreactive with EO and could be used as a barrier material in the claimed method of EO sterilization. The tertiary reference to Lambert does not overcome the deficiencies of Jones and Gordon to suggest the claimed invention.

Withdrawal of the §103 rejection is respectfully requested.

## CONCLUSION

Applicants respectfully submit that claims 1-10 are in condition for allowance, which action is earnestly solicited. Authorization is hereby given to charge any fee which may be due in connection with this communication to Deposit Account 23-1703.

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Respectfully submitted,

John M. Genova
Reg. No. 32,224
Attorney

Customer Number: 007470
Direct Dial: (212) 819-8832

Attachment: Medical Plastics: Data Services,
http://www.medicalplasticsindia.com/mpds/2002/may/packaging.htm (3 pages)

MEDICAL PLASTICS
DATA SERVICE
A TECHNO-ECONOMIC NEWS MAGAZINE FOR MEDICAL PLASTICS AND PHARMACEUTICAL INDUSTRY
Our 9th Year of Publication

# Packaging : ETO Sterilization and Packaging

[Sandeep Kumar Goyal, Rexam Packaging (India) Ltd]

Sterility is defined as complete freedom from all viable microorganisms. The process of sterilization is a probability function, because of the logarithmic order of microbial death and the less than absolute methods of confirming sterility.

Sterilization can be done by various methods like :

1. Steam sterilization
2. Radiation sterilization
3. E beam sterilization
4. Gaseous sterilization
5. Chemical sterilization

ETO sterilization, type of gaseous sterilization is also known as EO or ethylene oxide gas sterilization. Every sterilization method has its own limitations of destroying microorganisms. Major factors that affect the utility of sterilization method-1 are :

1. Its compatibility with the product, material or substance being sterilized.
2. Acceptability of the packaging.
3. Penetration of the agent to remote areas that may contain viable microorganisms.
4. High level of lethal activity resulting in the need for only low quantities of the sterilizing agent.
5. Relatively inexpensive.
6. High degree of safety and low toxicity.
7. Simplicity
8. Time required for the process; and
9. Adaptability to in-line processing.

**ETO sterilization**

Ethylene oxide has been used as an insecticide, pesticide and sterilizing medium for spices, gums and (latterly

medical devices) since 1928. Today it is quite common to use this as a sterilant and many a times along with inert gas.

During World War II, work was conducted by the Chemical Corps of the US army and a number of papers were then published by Phillips and Kaye, thoroughly reviewing the use of ethylene oxide as a decontainant and fumigant. The method of action of ethylene oxide is a complex interaction of a number of important factors. The mechanism of action of ethylene oxide is commonly attributed to its alkylating properties. A hydrogen atom may be replaced by an alkyl group. Ethylene oxide may also react with a carboxylic acid to form a longer chain hydrocarbon and free a hydrogen radical. ETO sterilization depends on following factors :

1. Chamber temperature
2. Relative humidity
3. Time of exposure
4. Concentration of the gas
5. Physical and chemical nature of the environment in which the microbial contaminants are located and the type and the number of microorganisms during gaseous ETO sterilization.

Microbial destruction occurs through the alkylation primarily of tertiary nitrogen groups and phosphoric acid esters of nucleic acid moieties. The chemical acts by alkylating the proteins of microorganisms, thereby upsetting their equilibrium. If the process is applied correctly, this reaction is irreversible, and reanimation of the alkylated microorganisms is prevented. Other than a minimal concentration of the gas itself, humidity (water vapor) is the most critical factor in any ETO sterilization process. Ethylene oxide (EO) is suitable for sterilizing heat labile articles that will withstand temperatures of 50-60oC. It is a method, which requires careful control in respect of its explosive characteristics, toxicity and for monitoring the efficiency of the process.

Kaye and Phillips established the initial quantitaion of the role of moisture in gaseous sterilization with ETO3 in 1949. Their data showed that the action of gaseous ETO sterilization in killing air dried spores of B subtilis var niger at 28% RG is about four times rapid as it is at 65% RH and almost 10 times as rapid as at 97% RH. If the bioburden has been desiccated, held at dry environmental conditions or held under high vacuum for a period of time, sterilization with gaseous ETO is increasingly difficult to achieve.

Spores dried on porous materials, such as paper and cloth are easier to sterilize than are spores dried on hard nonporous objects such as glass, metal and plastics.

The presence of various salts in the suspending medium from which materials have been dried also makes the destruction of the spores more difficult. The inability to achieve sterilization at very low moisture levels may be due in part to poor gas penetration. It is more likely a blockage of the alkylating action of ETO which requires the presence of water to allow ionization of hydrogen from nucleic acid or protein molecules before they react with ETO.

The importance of relative humidity to ethylene oxide sterilization is such that humidity of less than 30% may cause failure of the process. The moisture content of the microbial cell is another important factor in gaseous sterilization. Gilbert et al demonstrated that excessive drying of bacterial cells will result in a nonuniform reaction to ethylene oxide, and to rehydrate, direct contact with water is necessary. In view of this property, moisture distribution and permeation should be controlled at approximately 50% relative humidity (40-70% is the optimum range) to minimize the potential for production of desiccated spores.

**Disadvantages of ETO gas and residue**

One of its main disadvantages is the potential for toxic residues to be left in products and materials that have been sterilized. The three most comon toxic residues of importance are ethylene oxide and two of its reaction products, ethylene chlorohydrin and ethylene glycol. For example, polyethylene retain 2 mg ethylene oxide per gram. In general sense, ethylene oxide toxicity is basically equivalent to that of ammonia; however, its additional reactivity and mutagenecity

require that elaborate safety precautions to be taken with the use of this sterilizing agent.

Ethylene oxide is a toxic gas, which irritates the mucosa, causing acute pulmonary edema in high concentrations. It has also shown adverse reproductive and transplacental effects. It can also contribute to chromosomal damage and cancer incidence.

**Selection of packaging materials**

For effective sterilization, selection of packaging material also plays important role apart from sterilization parameters. This can be best done in consultation of packaging material suppliers. The following are keys in selecting a suitable packaging material for gas sterilization:

1. The packaging material must be permeable enough for ethylene oxide and moisture to enter the package (and air escape) and sterilize the contents within the desired cycle time: the penetration rate must be uniform. Productivity requirements make short cycles (high porosity) desirable.
2. The packaging material must be impermeable to bacteria and other contaminants.
3. The packaging material must not be deformed or porosity altered by pressure variations during vacuum cycles.

All plastic films used for wrapping should be evaluated on their ability to allow reasonable permeation of ethylene oxide gas, moisture, and air before and after sterilization. It has been observed that Medical Grade Paper on one side helps in faster aeration of EO Gas than laminate on both the sides. Permeability is one of the most important criteria. Not only must be sterilant be able to permeate the package, but the packaging material must have sufficient breathability to permit release of toxic residues (e.g. ethylene oxide residual gas). Additionally, the porosity and bond strength (the seal, or bond, between two packaging sub-strates) must be adequate enough to maintain package integrity.

For proper and safe ETO sterilization of medical devices, packaging materials and sterilization parameters go together. They need careful monitoring and selection.

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